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(BUSCHMANN-IVO-R$.IN.).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	2

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

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L5	Buschmann-Ivo-R$.in.	2	L5
L4	L3 and (ischemic or ischemia)	265	L4
L3	L2 and (VEGF or GM-CSF or G-CSF or M-CSF or SCF or SDF-1 or angiopoietin or (FLT-3 adj ligand))	530	L3
L2	(endothelial adj progenitor) or EPC	6388	L2
L1	Isner-Jeffrey-M$.in.	31	L1

PALM INTRANET

Day : Wednesday

Date: 7/19/2006
Time: 14:34:24

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Additionally, enter the **first few letters** of the Inventor's First name.

Last Name	First Name	
Asahara	Takayuki	Search

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PALM INTRANET

Day : Wednesday

Date: 7/19/2006
Time: 14:34:24

Inventor Name Search

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Last Name	**First Name**	
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***Inspec (File 202)

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***File 523, D&B European Dun's Market Identifiers
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Cost is in DialUnits
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B 155,5,73
       19jul06 13:57:53 User259876 Session D896.1
            $0.81    0.232 DialUnits File1
     $0.81  Estimated cost File1
     $0.05  INTERNET
     $0.86  Estimated cost this search
     $0.86  Estimated total session cost   0.232 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2006/Jul 18
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S (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR MOUSE OR RAT OR HUMAN O
Processing
          325560  ISCHEMIC
          387047  ISCHEMIA
          154645  MAMMAL
           94630  RODENT
           66358  PRIMATE
         1767564  MOUSE
         2969746  RAT
        14272661  HUMAN
         3699493  PATIENT
      S1  127734  (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE
                  OR MOUSE OR RAT OR HUMAN OR PATIENT)
?

S S1 AND (ANGIOGENESIS)
          127734  S1
           90041  ANGIOGENESIS
      S2    2124  S1 AND (ANGIOGENESIS)
?

S S2 NOT PY>1999
            2124  S2
        10427475  PY>1999
      S3     391  S2 NOT PY>1999
?

S S3 AND (GM-CSF OR G-CSF OR M-CSF)
             391  S3
            3505  GM-CSF
            1205  G-CSF
             332  M-CSF
      S4       0  S3 AND (GM-CSF OR G-CSF OR M-CSF)
?


Set     Items   Description
S1     127734   (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR
              MOUSE OR RAT OR HUMAN OR PATIENT)
S2       2124   S1 AND (ANGIOGENESIS)
S3        391   S2 NOT PY>1999
S4          0   S3 AND (GM-CSF OR G-CSF OR M-CSF)
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B 155, 5, 73
       19jul06 14:02:31 User259876 Session D896.2
            $1.73    0.508 DialUnits File155
     $1.73  Estimated cost File155
            $6.59    1.117 DialUnits File5
     $6.59  Estimated cost File5
            $9.29    0.829 DialUnits File73
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      $9.29  Estimated cost File73
             OneSearch, 3 files,  2.454 DialUnits FileOS
      $1.33  INTERNET
     $18.94  Estimated cost this search
     $19.80  Estimated total session cost   2.686 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2006/Jul 18
         (c) format only 2006 Dialog
  File   5:Biosis Previews(R) 1969-2006/Jul W3
         (c) 2006 The Thomson Corporation
  File  73:EMBASE 1974-2006/Jul 19
         (c) 2006 Elsevier Science B.V.

       Set  Items  Description
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S (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR MOUSE OR RAT OR RABBIT
           325560  ISCHEMIC
           387047  ISCHEMIA
           154645  MAMMAL
            94630  RODENT
            66358  PRIMATE
          1767564  MOUSE
          2969746  RAT
           601944  RABBIT
          3699493  PATIENT
       S1  105658  (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE
                   OR MOUSE OR RAT OR RABBIT OR PATIENT)
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S S1 AND (ANGIOGENESIS)
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            90041  ANGIOGENESIS
       S2    1556  S1 AND (ANGIOGENESIS)
?

S S2 NOT PY>1999
             1556  S2
         10427475  PY>1999
       S3     293  S2 NOT PY>1999
?

S S3 AND (GM-CSF OR G-CSF OR M-CSF OR VEGF)
              293  S3
             3505  GM-CSF
             1205  G-CSF
              332  M-CSF
            43163  VEGF
       S4     125  S3 AND (GM-CSF OR G-CSF OR M-CSF OR VEGF)
?

RD
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?

S S5 NOT PY>1998
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         11881981  PY>1998
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      S6       42  S5 NOT PY>1998
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Set     Items   Description
S1     105658   (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR
             MOUSE OR RAT OR RABBIT OR PATIENT)
S2       1556   S1 AND (ANGIOGENESIS)
S3        293   S2 NOT PY>1999
S4        125   S3 AND (GM-CSF OR G-CSF OR M-CSF OR VEGF)
S5         57   RD  (unique items)
S6         42   S5 NOT PY>1998
?

S S3 AND (SCF OR SDF-1)
            293  S3
          11670  SCF
            363  SDF-1
      S7      0  S3 AND (SCF OR SDF-1)
?

S S3 AND (ANGIOPOIETIN-1 OR ANGIOPOIETIN-2 OR (FLT-3 (W) LIGAND))
            293  S3
           1103  ANGIOPOIETIN-1
            834  ANGIOPOIETIN-2
            145  FLT-3
         347577  LIGAND
              0  FLT-3(W)LIGAND
      S8      1  S3 AND (ANGIOPOIETIN-1 OR ANGIOPOIETIN-2 OR (FLT-3 (W)
                 LIGAND))
?

T S8/3,K/ALL

  8/3,K/1      (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0012264555   BIOSIS NO.: 199900524215
 Angiopoietin-1 potentiates angiogenic response to vascular endothelial
 growth factor (VEGF) in hypercholesterolemic rabbit model with acute
 hindlimb ischemia
AUTHOR: Shyu Kou-Gi (Reprint); Silver Marcy (Reprint); Magner Meredith
  (Reprint); Yancopoulos George D; Isner Jeffrey M (Reprint)
AUTHOR ADDRESS: St. Elizabeth's Med. Cent., Boston, MA, USA**USA
JOURNAL: Circulation  98 (17 SUPPL.): pI464 Oct. 27, 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart
Association  Dallas, Texas, USA  November 8-11, 1998; 19981108
SPONSOR: The American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

 Angiopoietin-1 potentiates angiogenic response to vascular endothelial
 growth factor (VEGF) in hypercholesterolemic  rabbit  model with acute
 hindlimb  ischemia
...REGISTRY NUMBERS:  angiopoietin-1
DESCRIPTORS:
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  CHEMICALS & BIOCHEMICALS:    angiopoietin-1 ...
  MISCELLANEOUS TERMS:    angiogenesis ;
?


Set     Items   Description
S1     105658   (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR
             MOUSE OR RAT OR RABBIT OR PATIENT)
S2       1556   S1 AND (ANGIOGENESIS)
S3        293   S2 NOT PY>1999
S4        125   S3 AND (GM-CSF OR G-CSF OR M-CSF OR VEGF)
S5         57   RD  (unique items)
S6         42   S5 NOT PY>1998
S7          0   S3 AND (SCF OR SDF-1)
S8          1   S3 AND (ANGIOPOIETIN-1 OR ANGIOPOIETIN-2 OR (FLT-3 (W) LIG-
             AND))
?

T S6/3,K/ALL

  6/3,K/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12085934   PMID: 10193309
 The  vascular  endothelial growth factor family; proteins which guide the
 development of the vasculature.
  Achen M G; Stacker S A
  Angiogenesis  Laboratory,  Ludwig  Institute  for  Cancer Research, Royal
Melbourne Hospital, Victoria, Australia. Marc.achen@ludwig.edu.au
  International journal of experimental pathology (ENGLAND)  Oct 1998,  79
  (5)  p255-65,  ISSN 0959-9673--Print   Journal Code: 9014042
  Publishing Model Print
  Document type: Journal Article; Review
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed

  The  development  of  the  vascular  tree  during  embryogenesis involves
vasculogenesis,   angiogenesis  and  tissue-specific  differentiation  of
endothelium which gives rise to many different vessel types. These...

...cell-specific receptors and cognate ligands has led to the generation of
transgenic  and  knockout  mouse  models  which  have  shed  light on the
molecular  mechanisms  that regulate the development of blood and lymphatic
vessels  during  embryogenesis.  Such  mouse  models have demonstrated that
members  of  the  vascular  endothelial  growth  factor  ( VEGF ) family of
proteins  and  the  VEGF  receptors  are  critical  regulators  of
vasculogenesis,  angiogenesis  and endothelial cell differentiation. The
availability  of  purified  VEGF  family members and of inhibitors of these
growth  factors may provide a means to modulate blood vessel growth for the
treatment of cancer, retinopathies and diseases of  ischemia.


  6/3,K/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12026817   PMID: 9860779
 Gene  therapy  for myocardial angiogenesis: initial clinical results with
```

direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia.

Losordo D W; Vale P R; Symes J F; Dunnington C H; Esakof D D; Maysky M; Ashare A B; Lathi K; Isner J M

Departments of Medicine, Biomedical Research, Surgery, and Anesthesiology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Mass 02135, USA.

Circulation (UNITED STATES) Dec 22-29 1998, 98 (25) p2800-4, ISSN 0009-7322--Print Journal Code: 0147763

Publishing Model Print

Document type: Case Reports; Clinical Trial; Clinical Trial, Phase I; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Gene therapy for myocardial angiogenesis : initial clinical results with direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia.

... determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (VEGF) as sole therapy for patients with symptomatic myocardial ischemia . METHODS AND RESULTS: VEGF gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who...

...these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding VEGF (phVEGF165) was injected directly into the ischemic myocardium via a mini left anterior thoracotomy. Injections caused no changes in heart rate (pre...

... the moment of injection. Serial ECGs showed no evidence of new myocardial infarction in any patient . Intraoperative blood loss was 0 to 50 cm3, and total chest tube drainage was 110...

... n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced ischemia was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients...

... 5 patients. CONCLUSIONS: This initial experience with naked gene transfer as sole therapy for myocardial ischemia suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall...

... may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial ischemia.

6/3,K/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11998706 PMID: 9828156

Increased expression of KDR/Flk-1 (VEGFR-2) in murine model of ischemia-induced retinal neovascularization.

Suzuma K; Takagi H; Otani A; Suzuma I; Honda Y

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, 606, Japan.

Microvascular research (UNITED STATES) Nov 1998, 56 (3) p183-91, ISSN 0026-2862--Print Journal Code: 0165035

Publishing Model Print

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Although the vascular endothelial growth factor (VEGF)/ VEGF receptor system plays a critical role in the pathogenesis of ischemic retinal neovascular diseases such as diabetic retinopathy, regulation of VEGF receptor expression in ischemic retina has not been fully investigated in vivo. Accordingly, we studied the regulation of Flt-1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2) expression in a mouse model of ischemia -induced retinal neovascularization. Immunohistochemistry for Flt-1 and KDR/Flk-1 revealed that, in hypoxic...

... suggest that the increased expression of KDR/Flk-1 in vascular cells might potentiate the VEGF -mediated angiogenesis that accompanies many ischemic retinal diseases. Copyright 1998 Academic Press.

6/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11924394 PMID: 9751672
Endothelium-dependent relaxation of collateral microvessels after intramuscular gene transfer of vascular endothelial growth factor in a rat model of hindlimb ischemia.
Takeshita S; Isshiki T; Ochiai M; Eto K; Mori H; Tanaka E; Umetani K; Sato T
Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan. stake@blue.ocn.ne.jp
Circulation (UNITED STATES) Sep 29 1998, 98 (13) p1261-3, ISSN 0009-7322--Print Journal Code: 0147763
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

... **relaxation of collateral microvessels after intramuscular gene transfer of vascular endothelial growth factor in a rat model of hindlimb ischemia.**
BACKGROUND: Recent investigations have demonstrated the ability of vascular endothelial growth factor (VEGF) to augment the development of collateral arteries in vivo. In vitro studies have suggested that the use of VEGF also improves the endothelium-dependent relaxation of collaterals at the microvascular level. The purpose of...

... determine in vivo the extent to which vasomotor responses of collateral microvessels are altered after VEGF treatment. METHODS AND RESULTS :Ischemia was induced in the hindlimb of 35 rats by excision of the femoral artery. Immediately thereafter, 400 microg of a plasmid encoding VEGF or ss-galactosidase (control) was transfected into limb muscles. Four weeks later, synchrotron radiation microangiography...

... microvessels in control animals. By contrast, profound dilation of collaterals was observed after acetylcholine in VEGF -treated animals. This response was evident in vessels with a linear appearance but not in...

... the contralateral normal limb, whereas blood flow was augmented to

106.1+/-8.4% in VEGF -treated animals (P<0.05). CONCLUSIONS: These results demonstrate in vivo that the use of VEGF restores impaired vasomotor responses in some types of collateral microvessels, which may help to provide a basis for understanding the microcirculation after therapeutic angiogenesis with VEGF.

6/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11905325 PMID: 9734840
Effect of time on the viability of ischemic skin flaps treated with vascular endothelial growth factor (VEGF) cDNA.
Taub P J; Marmur J D; Zhang W X; Senderoff D; Urken M L; Silver L; Weinberg H
Department of Otolaryngology, and Cardiovascular Institute, Mt. Sinai Medical Center, New York, NY 10029, USA.
Journal of reconstructive microsurgery (UNITED STATES) Aug 1998, 14 (6) p387-90, ISSN 0743-684X--Print Journal Code: 8502670
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

...of time on the viability of ischemic skin flaps treated with vascular endothelial growth factor (VEGF) cDNA.
... investigated whether delivery of the gene encoding a particular cytokine, known to be important in angiogenesis , could affect ischemic skin flaps. Anterior abdominal skin flaps, based solely on the epigastric artery and vein, were created in the Sprague-Dawley rat model. At the time of elevation, the arterial pedicle supplying each flap was infused either with the gene for vascular endothelial growth factor (VEGF) or physiologic saline alone. The flaps were resutured into place and observed for a period...

... was subsequently measured by planimetry after a period of 7 days. Flaps that received the VEGF gene and were ligated at 4 days had an average dye fluorescence index (DFI) of...

...1 for the saline-infused group. The results suggest that delivery of the gene for VEGF can improve the survival of ischemic skin flaps, but that the effect of gene therapy is not limitless.

6/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11879969 PMID: 9708799
Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis in the setting of tissue ischemia.
Witzenbichler B; Asahara T; Murohara T; Silver M; Spyridopoulos I; Magner M; Principe N; Kearney M; Hu J S; Isner J M
Department of Medicine, St. Elizabeth's Medical Center of Boston, Tufts University School of Medicine, Massachusetts 02135, USA.
American journal of pathology (UNITED STATES) Aug 1998, 153 (2) p381-94, ISSN 0002-9440--Print Journal Code: 0370502
Publishing Model Print

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor-C (VEGF -C/ VEGF -2) promotes angiogenesis in the setting of tissue ischemia.

Recently, vascular endothelial growth factor-C (VEGF -C or VEGF -2) was described as a specific ligand for the endothelial receptor tyrosine kinases VEGFR-2...
... overexpression in transgenic mice, have been interpreted as evidence that the growth-promoting effects of VEGF -C are restricted to development of the lymphatic vasculature. The current studies were designed to test the hypothesis that constitutive expression of VEGF -C in adult animals promotes angiogenesis . In vitro, VEGF -C exhibited a dose-dependent mitogenic and chemotactic effect on endothelial cells, particularly for microvascular endothelial cells (72% and 95% potency, respectively, compared with VEGF -A/ VEGF -1). VEGF -C stimulated release of nitric oxide from endothelial cells and increased vascular permeability in the...

... shown to be expressed in human saphenous vein and internal mammary artery. The potential for VEGF -C to promote angiogenesis in vivo was then tested in a rabbit ischemic hindlimb model. Ten days after ligation of the external iliac artery, VEGF -C was administered as naked plasmid DNA (pcVEGF-C; 500 microg) from the polymer coating...

... protein (rhVEGF-C; 500 microg) by direct intra-arterial infusion. Physiological and anatomical assessments of angiogenesis 30 days later showed evidence of therapeutic angiogenesis for both pcVEGF-C and rhVEGF-C. Hindlimb blood pressure ratio (ischemic /normal) after pcVEGF-C increased to 0.83 +/- 0.03 after pcVEGF-C versus 0...
... after rhVEGF-C versus 0.58 +/- 0.03 ($P < 0.01$) in control rabbits receiving rabbit serum albumin. Doppler-derived iliac flow reserve was 2.7 +/- 0.1 versus 2.0...

... 05) for protein). In contrast to the results of gene targeting experiments, constitutive expression of VEGF -C in adult animals promotes angiogenesis in the setting of limb ischemia . VEGF -C and its receptors thus constitute an apparently redundant pathway for postnatal angiogenesis and may represent an alternative to VEGF -A for strategies of therapeutic angiogenesis in patients with limb and/or myocardial ischemia.

6/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11872907 PMID: 9701350
Reduction of ischemic damage by application of vascular endothelial growth factor in rat brain after transient ischemia.
Hayashi T; Abe K; Itoyama Y
Department of Neurology, Tohoku University School of Medicine Sendai, Japan.
Journal of cerebral blood flow and metabolism - official journal of the International Society of Cerebral Blood Flow and Metabolism (UNITED STATES) Aug 1998, 18 (8) p887-95, ISSN 0271-678X--Print Journal Code: 8112566
Publishing Model Print
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Reduction of ischemic damage by application of vascular endothelial growth factor in rat brain after transient ischemia.

Vascular endothelial growth factor (VEGF) is a secreted polypeptide and plays a pivotal role in angiogenesis in vivo. However, it also increases vascular permeability, and might exacerbate ischemic brain edema. The effect of this factor on the brain after transient ischemia was investigated in terms of infarct volume and edema formation, as well as cellular injury. After 90 minutes of transient middle cerebral artery occlusion, VEGF (1.0 ng/microL, 9 microL) was topically applied on the surface of the reperfused rat brain. A significant reduction of infarct volume was found in animals with VEGF application ($P < 0.001$) at 24 hours of reperfusion as compared with cases with vehicle treatment. Brain edema was significantly reduced in VEGF -treated animals ($P = 0.01$), and furthermore, extravasation of Evans blue was also decreased in...

...protein showed an amelioration of the stainings at 24 and 48 hours after reperfusion with VEGF treatment, which indicated reduction of neuronal damage. These results indicate that treatment with topical VEGF application significantly reduces ischemic brain damage, such as infarct volume, edema formation, and extravasation of Evans blue, and that...

6/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11855464 PMID: 9682821
Vascular endothelial growth factor expression in transient focal cerebral ischemia in the rat.
Cobbs C S; Chen J; Greenberg D A; Graham S H
Department of Neurosurgery, University of Alabama, Birmingham, USA.
Neuroscience letters (IRELAND) Jun 19 1998, 249 (2-3) p79-82, ISSN 0304-3940--Print Journal Code: 7600130
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor expression in transient focal cerebral ischemia in the rat.

Vascular endothelial growth factor (VEGF) has been implicated in hypoxia-induced angiogenesis in tumors and ischemia. We examined VEGF mRNA and protein expression after occlusion of the middle cerebral artery (MCA) in rats. VEGF mRNA expression studied by in situ hybridization was increased in the ischemic border zone 24 h after 30, 60 or 120 min of focal cerebral ischemia. VEGF protein expression measured by Western blots was also increased in this region 24 and 48 h after ischemia, and VEGF immunocytochemistry localized this increased expression to astroglia. Thus, VEGF is induced after focal cerebral ischemia and could have a role in pathophysiology and recovery...

6/3,K/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11803286 PMID: 9626071
Mouse model of angiogenesis.
Couffinhal T; Silver M; Zheng L P; Kearney M; Witzenbichler B; Isner J M
Department of Medicine (Cardiology), St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston Massachusetts 02135, USA.
American journal of pathology (UNITED STATES) Jun 1998, 152 (6) p1667-79, ISSN 0002-9440--Print Journal Code: 0370502
Contract/Grant No.: HL02824; HL; NHLBI; HL40518; HL; NHLBI; HL57516; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Mouse model of angiogenesis.
Neovascularization of ischemic muscle may be sufficient to preserve tissue integrity and/or function and may thus be considered to be therapeutic. The regulatory role of vascular endothelial growth factor (VEGF) in therapeutic angiogenesis was suggested by experiments in which exogenously administered VEGF was shown to augment collateral blood flow in animals and patients with experimentally induced hindlimb or myocardial ischemia . To address the possible contribution of postnatal endogenous VEGF expression to collateral vessel development in ischemia tissues, we developed a mouse model of hindlimb ischemia . The femoral artery of one hindlimb was ligated and excised. Laser Doppler perfusion imaging (LDPI ...

... for bromodeoxyuridine injected 24 hours before each of these time points, providing additional evidence that angiogenesis constitutes the basis for improved collateral-dependent flow in this animal model. Neovascularization was shown to develop in association with augmented expression of VEGF mRNA and protein from skeletal myocytes as well as endothelial cells in the ischemic hindlimb; that such reparative angiogenesis is indeed dependent upon VEGF up-regulation was confirmed by impaired neovascularization after administration of a neutralizing VEGF antibody. Sequential characterization of the in vivo, histological, and molecular findings in this novel animal model thus document the role of VEGF as endogenous regulator of angiogenesis in the setting of tissue ischemia . Moreover, this murine model represents a potential means for studying the effects of gene targeting on nutrient angiogenesis in vivo.

6/3,K/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11697788 PMID: 9500609
Vascular endothelial growth factor is essential for corpus luteum angiogenesis.
Ferrara N; Chen H; Davis-Smyth T; Gerber H P; Nguyen T N; Peers D; Chisholm V; Hillan K J; Schwall R H
Department of Cardiovascular Research, Genentech Inc., South San Francisco, California 94080, USA. Ferrara.Napoleone@gene.com
Nature medicine (UNITED STATES) Mar 1998, 4 (3) p336-40, ISSN 1078-8956--Print Journal Code: 9502015
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor is essential for corpus luteum angiogenesis.

... growth of new capillary vessels. Although several molecules have been implicated as mediators of CL angiogenesis , at present there is no direct evidence for the involvement of any. Here we report...
... finding that treatment with truncated soluble Flt-1 receptors, which inhibit vascular endothelial growth factor (VEGF) bioactivity, resulted in virtually complete suppression of CL angiogenesis in a rat model of hormonally induced ovulation. This effect was associated with inhibition of CL development and progesterone release. Failure of maturation of the endometrium was also observed. Areas of ischemic necrosis were demonstrated in the corpora lutea (CLs) of treated animals. However, no effect on...

... vasculature was observed. These findings demonstrate that, in spite of the redundancy of potential mediators, VEGF is essential for CL angiogenesis . Furthermore, they have implications for the control of fertility and the treatment of ovarian disorders...

6/3,K/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11678295 PMID: 9468212
Potentiated angiogenic effect of scatter factor/hepatocyte growth factor via induction of vascular endothelial growth factor: the case for paracrine amplification of angiogenesis.
Van Belle E; Witzenbichler B; Chen D; Silver M; Chang L; Schwall R; Isner J M
Department of Medicine (Cardiology), St Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Mass 02135, USA.
Circulation (UNITED STATES) Feb 3 1998, 97 (4) p381-90, ISSN 0009-7322--Print Journal Code: 0147763
Contract/Grant No.: HL-40518; HL; NHLBI; HL-53354; HL; NHLBI; HL-57516; HL; NHLBI; +
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

...growth factor via induction of vascular endothelial growth factor: the case for paracrine amplification of angiogenesis.
...the effects of recombinant human (rh) SF/HGF in vitro and in vivo in a rabbit model of hindlimb ischemia . We further compared these effects with those of recombinant human vascular endothelial growth factor (rhVEGF165...

...migration. Application of rhSF/HGF to cultures of human SMCs resulted in the induction of VEGF mRNA and protein. In vivo, administration of rhSF/HGF (500 microg x 3) was associated...

... pronounced than those of rhVEGF165 administered according to the same protocol (P<.05). Neither remote angiogenesis nor other pathological sequelae were observed with either rhSF/HGF or rhVEGF165. CONCLUSIONS: The pleiotropic effects of certain growth factors may potentiate angiogenesis

via a combination of direct effects on EC proliferation and migration and indirect effects that...

... potent EC mitogens from non-EC populations. The synergistic effects demonstrated when SF/HGF and VEGF are administered together in vitro may be reproduced in vivo by SF/HGF-induced upregulation of VEGF in vascular SMCs.

6/3,K/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11675790 PMID: 9462772
Vascular endothelial growth factor expression in expanded tissue: a possible mechanism of angiogenesis in tissue expansion.
Lantieri L A; Martin-Garcia N; Wechsler J; Mitrofanoff M; Raulo Y; Baruch J P
Department of Plastic Surgery, Henri Mondor Hospital, Paris XII University, Creteil, France.
Plastic and reconstructive surgery (UNITED STATES) Feb 1998, 101 (2) p392-8, ISSN 0032-1052--Print Journal Code: 1306050
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor expression in expanded tissue: a possible mechanism of angiogenesis in tissue expansion.
Vascular endothelial growth factor (VEGF) is a major angiogenic growth factor. Angiogenesis stimulated by VEGF occurs in several important clinical contexts, including myocardial ischemia , retinal disease, and tumor growth. The level of VEGF is increased in several skin disorders and is stimulated by ischemia . Tissue expansion has been shown to induce angiogenesis and ischemia on the overlying skin. We therefore investigated the hypothesis that VEGF was expressed in expanded tissue. Three samples of skin were obtained from five patients who...

... the expanded skin on the site of expansion. On these samples we performed immunolocalization of VEGF . Mouse monoclonal antibody was used, recognized with rabbit anti- mouse immunoglobulin alkaline phosphatase-anti-alkaline phosphatase (APAAP) complex conjugated and revealed with naphthol red. Our results showed clearly an increased number of cells that fixated VEGF antibody on the site of expansion. Cell counts revealed that the numbers of cells expressing VEGF were statistically higher in expanded tissue than in nonexpanded tissue. Before expansion skin specimens did not express VEGF . These findings are the first to show the presence of a growth factor in expanded tissue. They open a new field of research on the biological explanation of tissue-expanded angiogenesis.

6/3,K/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11602926 PMID: 9463639
Activation of Flk-1/KDR mediates angiogenesis but not hypotension.
Malavaud B; Tack I; Jonca F; Praddaude F; Moro F; Ader J L; Plouet J
Laboratoire de Biologie Moleculaire Eucaryote/UPR CNRS 9006, Toulouse,

France.
Cardiovascular research (NETHERLANDS) Nov 1997, 36 (2) p276-81, ISSN 0008-6363--Print Journal Code: 0077427
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Activation of Flk-1/KDR mediates angiogenesis but not hypotension.

OBJECTIVE: The concept of therapeutic angiogenesis with vascular endothelial growth factor (VEGF) has been validated in peripheral arterial disease. Its use in myocardial ischemia may be delayed as the result of the description in a porcine model of peripheral vasodilation after intraluminal injections of VEGF resulting in a 50% fatality rate by hypotension. We carried out this study to test whether VEGF -induced hypotension (1) is species specific, (2) is mediated by the receptor mediating angiogenesis , (3) is prevented by inhibition of nitric oxide synthase. METHODS: In the rabbit corneal pocket assay we tested whether a previously published anti-idiotypic antibody (AIA) agonist of the VEGF receptor Flk-1/KDR could elicit angiogenesis . Various doses of recombinant VEGF or AIA were injected into anesthetized normotensive Wistar-Kyoto rats and the mean arterial blood pressure (MABP) was recorded. To test the implication of nitric oxide in VEGF -induced hypotension we treated the animals with a competitive inhibitor of nitric oxide synthase prior to the injection of VEGF . RESULTS: Both VEGF and AIA induce angiogenesis but only intravenous injections of VEGF induced a rapid, transient and dose-dependent decrease in MABP. The ED50 was 0.5 micrograms. The interval between two VEGF injections required to lead to a decrease of MABP was 40 minutes. Nitric oxide synthesis inhibitor prevented, in a reversible fashion, the effect of VEGF . CONCLUSION: VEGF -induced hypotension is not species specific. It is prevented by nitric oxide inhibition. VEGF -induced angiogenesis and hypotension are not mediated in vivo by the same VEGF receptor.

6/3,K/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11523156 PMID: 9377574

Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders.

Presta L G; Chen H; O'Connor S J; Chisholm V; Meng Y G; Krummen L; Winkler M; Ferrara N
Department of Immunology, Genentech, Inc., South San Francisco, California 94080, USA.
Cancer research (UNITED STATES) Oct 15 1997, 57 (20) p4593-9, ISSN 0008-5472--Print Journal Code: 2984705R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor (VEGF) is a major mediator of angiogenesis associated with tumors and other pathological conditions, including proliferative diabetic retinopathy and age-related macular degeneration. The murine anti-human VEGF monoclonal antibody (muMAb VEGF) A.4.6.1 has been shown to potently suppress angiogenesis and growth in

a variety of human tumor cells lines transplanted in nude mice and also to inhibit neovascularization in a primate model of ischemic retinal disease. In this report, we describe the humanization of muMAb VEGF A.4.6.1. by site-directed mutagenesis of a human framework. Not only the ...

... determining regions but also several framework residues were changed from human to murine. Humanized anti- VEGF F(ab) and IgG1 variants bind VEGF with affinity very similar to that of the original murine antibody. Furthermore, recombinant humanized MAb VEGF inhibits VEGF -induced proliferation of endothelial cells in vitro and tumor growth in vivo with potency and efficacy very similar to those of muMAb VEGF A.4.6.1. Therefore, recombinant humanized MAb VEGF is suitable to test the hypothesis that inhibition of VEGF -induced angiogenesis is a valid strategy for the treatment of solid tumors and other disorders in humans.

6/3,K/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11516248 PMID: 9354516
Vascular endothelial growth factor attenuates myocardial ischemia-reperfusion injury.
Luo Z; Diaco M; Murohara T; Ferrara N; Isner J M; Symes J F
Department of Surgery, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts 02135-2997, USA.
Annals of thoracic surgery (UNITED STATES) Oct 1997, 64 (4) p993-8, ISSN 0003-4975--Print Journal Code: 15030100R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

BACKGROUND: Hypoxic endothelial cell activation plays a key role in the myocardial dysfunction resulting from ischemia -reperfusion injury. Recent evidence suggests that vascular endothelial growth factor (VEGF) may, in addition to promoting angiogenesis , modulate various aspects of endothelial function and repair. We examined whether administration of VEGF in the cardioplegic solution might have a beneficial effect on myocardial ischemia -reperfusion injury in an isolated rat heart model. METHODS: Hearts from Sprague-Dawley rats were perfused with Krebs-Henseleit solution in...

...work, and percent increase in coronary vascular resistance were measured after 2 hours of global ischemia and 40 minutes of reperfusion. Coronary effluent was collected after ischemia and reperfusion for measurement of creatine kinase. RESULTS: Hearts receiving cardioplegia solution containing 125 microg VEGF showed significantly improved recovery of cardiac output, coronary flow, and stroke work, and significantly reduced...

... hyperkalemic cardioplegia only ($p < 0.05$). Coadministration of a nitric oxide synthase inhibitor attenuated the VEGF -induced cardiprotective effects. Hearts treated with VEGF released significantly less creatine kinase compared with control hearts. CONCLUSIONS: Addition of VEGF to hyperkalemic cardioplegia protects against myocardial ischemia -reperfusion injury in the isolated rat heart.

6/3,K/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11507921 PMID: 9342366
Intracerebral tumor-associated hemorrhage caused by overexpression of the vascular endothelial growth factor isoforms VEGF121 and VEGF165 but not VEGF189.
Cheng S Y; Nagane M; Huang H S; Cavenee W K
Ludwig Institute for Cancer Research, San Diego Branch, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0660, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 28 1997, 94 (22) p12081-7, ISSN 0027-8424 --Print Journal Code: 7505876
Contract/Grant No.: HL09391-02; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The vascular endothelial growth factor (VEGF) has been shown to be a significant mediator of angiogenesis during a variety of normal and pathological processes, including tumor development. Human U87MG glioblastoma cells express the three VEGF isoforms: VEGF121, VEGF165, and VEGF189. Here, we have investigated whether these three isoforms have distinct roles in glioblastoma angiogenesis . Clones that overexpressed each isoform were derived and inoculated into mouse brains. Mice that received VEGF121- and VEGF165-overexpressing cells developed intracerebral hemorrhages after 60-90...

... none on the border of the tumors caused by the parental cells. Thus, by introducing VEGF -overexpressing glioblastoma cells into the brain, we have established a reproducible and predictable in vivo...

... of single molecular species. Such a model should be useful for uncovering the role of VEGF isoforms in the mechanisms of angiogenesis and for investigating intracerebral hemorrhage due to ischemic stroke or congenital malformations.

6/3,K/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11377584 PMID: 9198238
Angiogenesis in embryos and ischemic diseases.
Breier G; Damert A; Plate K H; Risau W
Department of Molecular Cell Biology, Max Planck Institute for Physiological and Clinical Research, Bad Nauheim, Germany. GBreier@kerckhoff.mpg.de
Thrombosis and haemostasis (GERMANY) Jul 1997, 78 (1) p678-83, ISSN 0340-6245--Print Journal Code: 7608063
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Angiogenesis in embryos and ischemic diseases.

...are thought to function as major regulators of blood vessel formation. Vascular endothelial growth factor (VEGF) and its receptors, Flt-1 (VEGFR-1) and Flk-1 (VEGFR-2), as well as...

... blood vessel formation during embryogenesis. Inactivation of any of the genes encoding these molecules in mouse embryos results in defective vascular development and embryonic lethality around mid-gestation. In addition, the VEGF signal transduction system has been implicated in the regulation of pathological blood vessel growth during certain angiogenesis -dependent diseases that are often associated with tissue ischemia , such as proliferative retinopathy or solid tumor growth. This hypothesis is substantiated by experiments, in which the inhibition of VEGF signal transduction resulted in the the inhibition of neovascularization in these diseases. Thus, the VEGF signal transduction system represents a useful target for an anti-angiogenic therapy.

6/3,K/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11288267 PMID: 9073561
Vascular endothelial growth factor is the major angiogenic factor in omentum: mechanism of the omentum-mediated angiogenesis.
Zhang Q X; Magovern C J; Mack C A; Budenbender K T; Ko W; Rosengart T K
Department of Cardiothoracic Surgery, New York Hospital-Cornell University Medical College, New York 10021, USA.
Journal of surgical research (UNITED STATES) Feb 1 1997, 67 (2) p147-54, ISSN 0022-4804--Print Journal Code: 0376340
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

... **endothelial growth factor is the major angiogenic factor in omentum: mechanism of the omentum-mediated angiogenesis.**
Omentum has been used clinically to promote wound healing and to stimulate the revascularization of ischemic tissues. The biologic mechanism responsible for these effects has, however, not yet been defined. A...
... responsible for the angiogenic properties of the omentum. The levels of vascular endothelial growth factor (VEGF) protein in a number of rat tissues and organs were analyzed by Western and enzyme immunoassay analysis. Because omentum was found to have the greatest VEGF concentrations of the tissues examined, antibody neutralization, transcription inhibition assays, and Northern blot analysis were...

... tissues extractions and primary tissue cultures of omentum to further characterize the functional significance of VEGF expression in these tissues. The omentum demonstrated the highest VEGF secretion rate as well as the highest concentration of VEGF protein of the various rat tissues and organs examined. Fractionation studies of the omentum furthermore demonstrated that omental adipocytes, rather than the stromal-vascular cells, were the primary source of VEGF protein. An endothelial cell mitogenic assay showed that a major portion of the mitogenic activity of heparin-binding proteins and conditioned media derived from omentum was abolished by VEGF antibody. Additional studies with the transcription inhibitor actinomycin-D furthermore demonstrated that the VEGF gene was continuously transcribed in the rat omental adipocytes. Incubation of the

omental adipocytes under hypoxic conditions induced approximately a 1.7-fold increase in VEGF protein expression, which was abolished by actinomycin-D. Northern blot analysis demonstrated that hypoxia resulted in upregulation of the VEGF mRNA in the hypoxia-cultured omental adipocytes, suggesting that the augmentation of VEGF expression in omental adipocytes by hypoxia occurs at the transcriptional level. These data suggest that VEGF is the major angiogenic factor produced by omentum and possibly underlies the mechanism of omentum-induced angiogenesis . Augmented expression of VEGF by omental cells under hypoxic conditions may furthermore reflect the mechanism responsible for enhancing the angiogenic activity of omentum in the setting of ischemia.

6/3,K/19 (Item 19 from file: 155)

11054719 PMID: 8878563

Therapeutic angiogenesis following arterial gene transfer of vascular endothelial growth factor in a rabbit model of hindlimb ischemia.

Takeshita S; Weir L; Chen D; Zheng L P; Riessen R; Bauters C; Symes J F; Ferrara N; Isner J M

Department of Medicine (Cardiology), St. Elizabeth's Medical Center of Boston, Tufts University School of Medicine, Massachusetts 02135, USA.

Biochemical and biophysical research communications (UNITED STATES) Oct 14 1996, 227 (2) p628-35, ISSN 0006-291X--Print Journal Code: 0372516
Contract/Grant No.: HL-02824; HL; NHLBI; HL-40518; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Therapeutic angiogenesis following arterial gene transfer of vascular endothelial growth factor in a rabbit model of hindlimb ischemia.

The plasmid phVEGF165, expressing the 165-amino-acid isoform of vascular endothelial growth factor (VEGF), an endothelial cell specific mitogen, was applied to the polymer coating of an angioplasty balloon...
...the calf blood pressure ratio (ischemic/normal limb) to 0.70 +/- 0.08 in the VEGF -transfected group vs 0.50 +/- 0.18 in controls ($p < 0.05$). These findings suggest...

6/3,K/20 (Item 20 from file: 155)

11014153 PMID: 8833917

Reactive oxygen intermediates increase vascular endothelial growth factor expression in vitro and in vivo.

Kuroki M; Voest E E; Amano S; Beerepoot L V; Takashima S; Tolentino M; Kim R Y; Rohan R M; Colby K A; Yeo K T; Adamis A P

Department of Surgery, Children's Hospital, Boston, Massachusetts 02115, USA.

Journal of clinical investigation (UNITED STATES) Oct 1 1996, 98 (7) p1667-75, ISSN 0021-9738--Print Journal Code: 7802877
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: MEDLINE; Completed

Elevated vascular endothelial growth factor (VEGF) levels are required for ocular and tumor angiogenesis in animal models. Ischemic hypoxia is strongly correlated with increased VEGF expression in these systems and is considered a physiologically relevant stimulus. Because ischemic hypoxia is often followed by reperfusion and reactive oxygen intermediate (ROI) generation, we examined the potential role of ROI in the control of VEGF gene expression. Human retinal pigment epithelial cells exposed to superoxide or hydrogen peroxide rapidly increased VEGF mRNA levels. Superoxide-associated mRNA increases were dose dependent, blocked by antioxidants, and associated with elevated VEGF protein levels in conditioned media. Increases in VEGF mRNA levels were also observed in cultured human melanoma and rat glioblastoma cells with superoxide or hydrogen peroxide. Cycloheximide prevented the ROI-associated increases in VEGF mRNA. Transcriptional inhibition with actinomycin D revealed an inducible increase in VEGF mRNA half-life, but nuclear run-on experiments showed no increase in VEGF transcriptional rate. Reoxygenation of human retinal pigment epithelial cells in vitro and ocular reperfusion in vivo increased retinal VEGF mRNA levels. Antioxidants prevented the reperfusion-associated VEGF mRNA increases in retina. We conclude that ROIs increase VEGF gene expression in vitro and during the reperfusion of ischemic retina in vivo. The ROI-associated increases are mediated largely through increases in VEGF mRNA stability.

6/3,K/21 (Item 21 from file: 155)

10953884 PMID: 8761851

Effects of vascular endothelial growth factor on hemodynamics and cardiac performance.

Yang R; Thomas G R; Bunting S; Ko A; Ferrara N; Keyt B; Ross J; Jin H
Department of Cardiovascular Research, Genentech, South San Francisco, CA 94080, USA.

Journal of cardiovascular pharmacology (UNITED STATES) Jun 1996, 27 (6) p838-44, ISSN 0160-2446--Print Journal Code: 7902492
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor (VEGF), a major regulator of angiogenesis , has therapeutic benefit in animal models of coronary or limb ischemia . However, the hemodynamic effects of VEGF have not been investigated. We examined the effects of VEGF on hemodynamics and cardiac performance. Mean arterial pressure (MAP), heart rate (HR), cardiac output, stroke...
... left ventricular (LV) dP/dt, and hematocrit were measured before and after intravenous injection of VEGF in conscious, instrumented rats. VEGF caused a dose-dependent reduction in MAP and an associated increase in HR. VEGF (250 micrograms/kg) significantly decreased cardiac output and stroke volume without affecting the inotropic state of the left ventricle, as determined by dP/dt. VEGF significantly increased hematocrit. Furthermore, VEGF did not affect contractility or HR in the isolated rat heart in vitro. The data suggest that the VEGF -induced decrease in cardiac output is due to reduced stroke volume, which may be caused...

... NAME), a nitric oxide (NO) synthase inhibitor, significantly attenuated the depressor and tachycardic responses to VEGF , suggesting that VEGF -induced hypotension may be mediated by NO.

6/3,K/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10930607 PMID: 8727509
Arterial gene transfer for therapeutic angiogenesis in patients with peripheral artery disease.
Isner J M; Walsh K; Symes J; Pieczek A; Takeshita S; Lowry J; Rosenfield K; Weir L; Brogi E; Jurayj D
Human gene therapy (UNITED STATES) May 20 1996, 7 (8) p959-88, ISSN 1043-0342--Print Journal Code: 9008950
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Arterial gene transfer for therapeutic angiogenesis in patients with peripheral artery disease.
... of arterial occlusion is too severe to permit relief of pain and/or healing of ischemic ulcers. No effective medical therapy is available for the treatment of such patients. The purpose of this clinical protocol is to document the safety of therapeutic angiogenesis achieved in this case by percutaneous catheter-based delivery of the gene encoding vascular endothelial growth factor (VEGF) in patients with PAD; and, as secondary objectives, investigate the bioactivity of this strategy to relieve rest pain and heal ischemic ulcers of the lower extremities. The rationale for this human protocol is based upon preclinical studies performed in a rabbit model of hindlimb ischemia . These studies are described in detail below and in the manuscripts enclosed in the Appendix to this proposal. In brief, a single intra-arterial bolus of VEGF recombinant human protein, delivered percutaneously to the ischemic limb via an intravascular catheter, resulted in angiographic, hemodynamic, physiologic, and histologic evidence of augmented...

... a hydrogel-coated balloon to deliver 400 micrograms of a plasmid containing the cDNA for VEGF to the internal iliac artery in the same animal model. Accordingly, we propose to administer arterial gene (VEGF) therapy to patients with rest pain and/or ischemic leg ulcers considered not to be candidates for conventional revascularization techniques. The dose of plasmid...

6/3,K/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10882144 PMID: 8656665
Vascular endothelial growth factor augments muscle blood flow and function in a rabbit model of chronic hindlimb ischemia.
Walder C E; Errett C J; Bunting S; Lindquist P; Ogez J R; Heinsohn H G; Ferrara N; Thomas G R
Department of Cardiovascular Research, South San Francisco, California 94080, USA.

Journal of cardiovascular pharmacology (UNITED STATES) Jan 1996, 27 (1) p91-8, ISSN 0160-2446--Print Journal Code: 7902492
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Vascular endothelial growth factor augments muscle blood flow and function in a rabbit model of chronic hindlimb ischemia.

... have shown that angiogenic factors can increase vascularity and improve blood pressure (BP) in an ischemic limb. Whether changes in these parameters are indicators of significant improvement in muscle function has not been demonstrated. In a rabbit model of hind limb ischemia , we measured blood flow in the extensor digitorum longus muscle (EDL) both at rest and...

... p < 0.01). At 28 days after a single administration of vascular endothelial growth factor (VEGF), stimulated muscle blood flow (3 mg/kg intravenously, i.v.) and muscle function [1 mg...

... hemodynamic responses in the contralateral limb and in the kidneys confirmed that the effects of VEGF were confined to the ischemic limb. The data agree with findings that angiogenic factors increase perfusion through angiogenesis . We hypothesized that neovascularization allows work-associated muscle hyperemia, resulting in a significant improvement in ...

; Angiogenesis Inducing Agents; Animals; Blood Flow Velocity--drug effects--DE; Chronic Disease; Endothelial Growth Factors--therapeutic...
Chemical Name: Angiogenesis Inducing Agents; Endothelial Growth Factors ; Lymphokines; Vascular Endothelial Growth Factor A; Vascular Endothelial Growth Factors

6/3,K/24 (Item 24 from file: 155)

10656397 PMID: 7586219

VEGF165 expressed by a replication-deficient recombinant adenovirus vector induces angiogenesis in vivo.

Muhlhauser J; Merrill M J; Pili R; Maeda H; Bacic M; Bewig B; Passaniti A ; Edwards N A; Crystal R G; Capogrossi M C
Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA.

Circulation research (UNITED STATES) Dec 1995, 77 (6) p1077-86, ISSN 0009-7330--Print Journal Code: 0047103
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

VEGF165 expressed by a replication-deficient recombinant adenovirus vector induces angiogenesis in vivo.

... of angiogenic factors via virus-mediated gene transfer may be useful in the treatment of ischemic disorders, the replication-deficient adenovirus (Ad) vector AdCMV.VEGF165 (where CMV is cytomegalovirus and VEGF is vascular endothelial growth factor) containing the cDNA for human VEGF165, a secreted endothelial cell-specific angiogenic growth factor, was

constructed. Human umbilical vein endothelial cells (HUVECs) and rat aorta smooth muscle cells (RASMCs) infected with AdCMV.VEGF165 (5 and 20 plaque-forming units [pfu] per cell) demonstrated VEGF mRNA expression and protein secretion into the supernatant. Furthermore, the conditioned medium from these cells enhanced vascular permeability in vivo. In contrast, neither VEGF mRNA nor secreted protein was found in uninfected HUVECs or RASMCs or in cells infected...

... was resuspended in 0.5 mL Matrigel and injected subcutaneously into mice. Immunohistochemical staining demonstrated VEGF in the tissues surrounding the Matrigel plugs containing AdCMV.VEGF165 up to 3 weeks after injection, whereas no VEGF was found in the control plugs with AdCMV.beta gal. Two weeks after injection, there...

... evidence of neovascularization in the tissues surrounding the Matrigel containing AdCMV.VEGF165, whereas no significant angiogenesis was observed in response to AdCMV.beta gal. Furthermore, the Matrigel plugs with AdCMV.VEGF165...

...may provide a useful strategy for efficient local delivery of VEGF165 in the treatment of ischemic diseases.

6/3,K/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10649669 PMID: 7479819
Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins.
Aiello L P; Pierce E A; Foley E D; Takagi H; Chen H; Riddle L; Ferrara N; King G L; Smith L E
Beetham Eye Institute, Boston, MA, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Nov 7 1995, 92 (23) p10457-61, ISSN 0027-8424 --Print Journal Code: 7505876
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF -receptor chimeric proteins.
... loss in the United States results from complications associated with retinal neovascularization in patients with ischemic ocular diseases such as diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity. Intraocular expression of the angiogenic protein vascular endothelial growth factor (VEGF) is closely correlated with neovascularization in these human disorders and with ischemia -induced retinal neovascularization in mice. In this study, we evaluated whether in vivo inhibition of VEGF action could suppress retinal neovascularization in a murine model of ischemic retinopathy. VEGF -neutralizing chimeric proteins were constructed by joining the extracellular domain of either human (Flt) or mouse (Flk) high-affinity VEGF receptors with IgG. Control chimeric proteins that did not bind VEGF were also used. VEGF -receptor chimeric proteins eliminated in vitro retinal endothelial cell growth stimulation by either VEGF ($P < 0.006$) or hypoxic conditioned

medium (P < 0.005) without affecting growth under nonstimulated conditions. Control proteins had no effect. To assess in vivo response, animals with bilateral retinal ischemia received intravitreal injections of VEGF antagonist in one eye and control protein in the contralateral eye. Retinal neovascularization was quantitated...

... 77% and 66%, respectively. No retinal toxicity was observed by light microscopy. These data demonstrate VEGF 's causal role in retinal angiogenesis and prove the potential of VEGF inhibition as a specific therapy for ischemic retinal disease.

6/3,K/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10486164 PMID: 7540233
Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases.
Pe'er J; Shweiki D; Itin A; Hemo I; Gnessin H; Keshet E
Department of Ophthalmology, Hadassah University Hospital, Jerusalem, Israel.
Laboratory investigation; a journal of technical methods and pathology (UNITED STATES) Jun 1995, 72 (6) p638-45, ISSN 0023-6837--Print
Journal Code: 0376617
Publishing Model Print; Comment in Lab Invest. 1995 Jun;72(6) 615-8; Comment in PMID 7540232
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

... environment. Prompted by our previous findings that the potent angiogenic factor, vascular endothelial growth factor (VEGF), is hypoxia-inducible, we used in situ hybridization techniques to examine the thesis that VEGF functions as the link between retinal ischemia and a pathologic, intraocular, angiogenic response. EXPERIMENTAL DESIGN: To gain molecular access to human material...

... enucleated at the time of ongoing neovascularization. This methodology identified cells that have up-regulated VEGF expression during natural progression of the indicated diseases. A rabbit model was also used to determine whether experimentally induced retinal ischemia leads to up-regulation of VEGF expression. RESULTS: Proliferation of vascular elements in proliferative diabetic retinopathy and neovascularization of the retina...

... retinal vein occlusion, retinal detachment, and intraocular tumors were always accompanied by induction of retinal VEGF expression. Furthermore, in each case, expression of VEGF was induced only in a particular layer of the retina (either the outer nuclear layer...

... layer, or the ganglion cell layer), matching the zones affected by impaired perfusion. In a rabbit model simulating retinal vein occlusion, elevated levels of VEGF mRNA were detected within a few days of experimental induction of retinal ischemia , exclusively in the ischemic region. CONCLUSIONS: VEGF may be one of the long anticipated factors linking retinal ischemia and intraocular angiogenesis . Irrespective of the cause of retinal ischemia , sustained overproduction of VEGF by ischemic retinal cells may promote retinal and iris neovascularization in

a number of neovascular eye diseases.

6/3,K/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10438537 PMID: 7728992
Regulation of vascular endothelial growth factor in cardiac myocytes.
Levy A P; Levy N S; Loscalzo J; Calderone A; Takahashi N; Yeo K T; Koren G; Colucci W S; Goldberg M A
Cardiology Division, Brigham and Women's Hospital, Boston, MA 02115, USA.
Circulation research (UNITED STATES) May 1995, 76 (5) p758-66, ISSN 0009-7330--Print Journal Code: 0047103
Contract/Grant No.: DK-45098; DK; NIDDK; HL-46005; HL; NHLBI; T32-HL-07604; HL; NHLBI; +
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

... flow and coronary blood flow compromised by coronary artery disease, thereby protecting the myocardium from ischemia . Collateral vessel formation is the result of angiogenesis . Vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF), is a secreted mitogen specific for endothelial cells and an extremely potent angiogenic factor. In the present study, VPF/ VEGF mRNA and protein were demonstrated to be markedly stimulated in primary rat cardiac myocytes in vitro in response to reduction of the oxygen tension to 1% or inhibition of the electron transport chain. Four isoforms of VPF/ VEGF were coordinately regulated by hypoxia, including a novel isoform not previously described. Phorbol ester and...

... stimulators of protein kinase C and calcium influx, respectively, were found to markedly increase VPF/ VEGF mRNA expression in cardiac myocytes. Forskolin, a potent stimulator of adenylate cyclase, produced a small but significant increase in VPF/ VEGF mRNA expression in the cardiac myocytes. However, only H7, an inhibitor of protein kinase C, inhibited the hypoxic induction of VPF/ VEGF mRNA; inhibitors of calcium influx and the calcium-calmodulin-dependent protein kinase II as well as inhibition of protein kinase A did not block the hypoxic induction of VPF/ VEGF mRNA. This suggests that more than one signal transduction pathway is involved in regulating VPF/ VEGF expression. The sensor that regulates the expression of hypoxia-responsive genes has been proposed to...

6/3,K/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10391221 PMID: 7531786
Site-specific therapeutic angiogenesis after systemic administration of vascular endothelial growth factor.
Bauters C; Asahara T; Zheng L P; Takeshita S; Bunting S; Ferrara N; Symes J F; Isner J M
Department of Medicine (Cardiology), St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston.
Journal of vascular surgery - official publication, the Society for Vascular Surgery and International Society for Cardiovascular Surgery,

North American Chapter (UNITED STATES) Feb 1995, 21 (2) p314-24; discussion 324-5, ISSN 0741-5214--Print Journal Code: 8407742
Contract/Grant No.: HL 02824; HL; NHLBI; HL 40518; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Site-specific therapeutic angiogenesis after systemic administration of vascular endothelial growth factor.

PURPOSE: Recent experimental studies have established the feasibility of therapeutic angiogenesis ; in all cases, this has been achieved with local administration of angiogenic growth factors. This...

...administration of an angiogenic growth factor specifically mitogenic for endothelial cells--vascular endothelial growth factor (VEGF)--could augment collateral vessel development in a rabbit ischemic hindlimb model. METHODS: Ten days after the ligation of the external iliac artery and excision...

... femoral arteries in one limb of New Zealand white rabbits, heparin (800 IU, n = 13), VEGF (1 mg, n = 3; 5 mg, n = 5), heparin (800 IU) + VEGF (1 mg, n = 5; 5 mg, n = 7), or saline solution (n = 8) was injected...

... and limb perfusion were assessed 10 and 30 days after treatment. RESULTS: Animals in both VEGF -treated groups had a significantly higher ($p < 0.01$) increase in calf blood pressure ratio at day 10 (control, 0.44 +/- 0.02; heparin, 0.47 +/- 0.02; VEGF , 0.60 +/- 0.01; heparin+ VEGF , 0.61 +/- 0.02) and day 30 (control, 0.49 +/- 0.05; heparin, 0.48 +/- 0.02; VEGF , 0.70 +/- 0.03; heparin+ VEGF , 0.73 +/- 0.03). Both VEGF -treated groups had a significantly higher ($p < 0.05$) angiographic score at day 30 (control, 0.28 +/- 0.01; heparin, 0.28 +/- 0.01; VEGF , 0.37 +/- 0.01; heparin+ VEGF , 0.38 +/- 0.02). Maximum flow reserve at day 30 in the ischemic limb was higher ($p < 0.05$) in VEGF -treated rabbits (control, 1.87 +/- 0.07; heparin, 1.92 +/- 0.08; VEGF , 2.42 +/- 0.16; heparin+ VEGF , 2.33 +/- 0.12). Capillary density was higher ($p < 0.01$) in the ischemic muscles of VEGF -treated rabbits (control, 156 +/- 10/mm2; heparin, 178 +/- 8/mm2; VEGF , 230 +/- 10/mm2; heparin+ VEGF , 233 +/- 8/mm2). CONCLUSIONS: This series of in vivo experiments demonstrates that intravenous administration of VEGF , with or without heparin, results in both anatomic and physiologic evidence of enhanced collateral vessel formation in the rabbit ischemic hindlimb. Single-bolus systemic administration of VEGF may be a feasible therapeutic strategy in patients with lower-extremity ischemia.

6/3,K/29 (Item 29 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10235469 PMID: 7977826

Rapid induction of vascular endothelial growth factor expression by transient ischemia in rat heart.

Hashimoto E; Ogita T; Nakaoka T; Matsuoka R; Takao A; Kira Y
Fourth Department of Internal Medicine, School of Medicine, University of Tokyo, Japan.

American journal of physiology (UNITED STATES) Nov 1994, 267 (5 Pt 2) pH1948-54, ISSN 0002-9513--Print Journal Code: 0370511
Publishing Model Print

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Rapid induction of vascular endothelial growth factor expression by transient ischemia in rat heart.

Vascular endothelial growth factor (VEGF or vascular permeability factor), a direct-acting, endothelial cell-specific mitogen, has been suggested to...

... maintenance of vasculatures in tumor neovascularization and in normal tissues. To investigate possible roles of VEGF in ischemic hearts, we studied induction of VEGF mRNA by ischemia and hypoxia using coronary artery-ligated hearts in vivo and perfused hearts and cultured myocardial cells in vitro. VEGF mRNA was potently induced by ischemia in the heart in vivo. In perfused hearts, maximum...

... was confirmed in perfused hearts and cultured myocardial cells. These results suggest that induction of VEGF mRNA is upregulated by oxygen deprivation in the heart and that not only infarction but also chronic ischemia in the clinical setting could induce VEGF as a potent angiogenesis factor to stimulate coronary collateral formation.

6/3,K/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10211347 PMID: 7525111

Intramuscular administration of vascular endothelial growth factor induces dose-dependent collateral artery augmentation in a rabbit model of chronic limb ischemia.

Takeshita S; Pu L Q; Stein L A; Sniderman A D; Bunting S; Ferrara N; Isner J M; Symes J F

Department of Medicine (Cardiology), St Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA 02135.

Circulation (UNITED STATES) Nov 1994, 90 (5 Pt 2) pII228-34, ISSN 0009-7322--Print Journal Code: 0147763

Contract/Grant No.: HL-02824; HL; NHLBI; HL-40518; HL; NHLBI

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Intramuscular administration of vascular endothelial growth factor induces dose-dependent collateral artery augmentation in a rabbit model of chronic limb ischemia.

... Despite major advances in both surgical and percutaneous revascularization techniques, limb salvage and relief of ischemic pain cannot be achieved in many patients with diffuse peripheral vascular disease. Vascular endothelial growth factor (VEGF) is a heparin-binding, endothelial cell-specific mitogen. Previous studies have suggested that VEGF is a regulator of naturally occurring physiological and pathological angiogenesis . In this study, the therapeutic potential of intramuscularly administered VEGF was investigated in a rabbit model of chronic hindlimb ischemia . METHODS AND RESULTS: Ischemia was induced in the hindlimb of 24 New Zealand White rabbits by ligation of the...

... artery and complete excision of the femoral artery. Ten days after the induction of limb ischemia (day 0), saline (group A, n = 7) or the 165-amino acid isoform of recombinant human VEGF (group B: 200 micrograms, n = 6; group C: 500 micrograms, n = 7; group D: 1000 micrograms, n = 4) was administered intramuscularly into the ischemic limb daily for 10 days. Angiography on day 30 after initiation of therapy revealed statistically significant dose-dependent augmentation of collateral vessels in the ischemic limb (angiographic score: group A, 13.0 +/- 1.1; group B, 21.2 +/- 1.8...

... Capillary density in the thigh muscles on day 30 was 1.6 times greater in VEGF groups versus controls (176 +/- 15.3 versus 113 +/- 27.3 per square millimeter, P < .05). Amelioration of the hemodynamic deficit in the ischemic limb was documented by calf systolic blood pressure ratio (group A, 0.52 +/- 0.02...

...7%; group B, 33.3%; group C, 14.3%; group D, 0%) was greater in VEGF -treated than in control animals, again in a dose-dependent fashion. CONCLUSIONS: These findings demonstrate...

... augmentation in limb perfusion accompanied by evidence of increased collateral formation after intramuscular administration of VEGF in ischemic rabbit hindlimbs. This study thus supports the hypothesis that administration of VEGF to stimulate angiogenesis may represent a new therapeutic modality in the management of arterial insufficiency.

6/3,K/31 (Item 31 from file: 155)

09988948 PMID: 7509344

Therapeutic angiogenesis. A single intraarterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model.

Takeshita S; Zheng L P; Brogi E; Kearney M; Pu L Q; Bunting S; Ferrara N; Symes J F; Isner J M
Department of Medicine (Cardiology), St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts 02135.

Journal of clinical investigation (UNITED STATES) Feb 1994, 93 (2) p662-70, ISSN 0021-9738--Print Journal Code: 7802877
Contract/Grant No.: HL-02824; HL; NHLBI; HL-40518; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Therapeutic angiogenesis . A single intraarterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model.

Vascular endothelial growth factor (VEGF) is a heparin-binding, endothelial cell-specific mitogen. Previous studies have suggested that VEGF is a regulator of naturally occurring physiologic and pathologic angiogenesis . In this study we investigated the hypothesis that the angiogenic potential of VEGF is sufficient to constitute a therapeutic effect. The soluble 165-amino acid isoform of VEGF was administered as a single intra-arterial bolus to the internal iliac artery of rabbits...

... excised to induce severe, unilateral hind limb ischemia. Doses of

500-1,000 micrograms of VEGF produced statistically significant augmentation of collateral vessel development by angiography as well as the number...

... amelioration of the hemodynamic deficit in the ischemic limb was significantly greater in animals receiving VEGF than in nontreated controls (calf blood pressure ratio, 0.75 +/- 0.14 vs. 0.48...

... artery) to the distal point of parent vessel (reentry artery) reconstitution in seven of nine VEGF -treated animals. These findings establish proof of principle for the concept that the angiogenic activity of VEGF is sufficiently potent to achieve therapeutic benefit. Such a strategy might ultimately be applicable to...

6/3,K/32 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012264555 BIOSIS NO.: 199900524215
Angiopoietin-1 potentiates angiogenic response to vascular endothelial growth factor (VEGF) in hypercholesterolemic rabbit model with acute hindlimb ischemia
AUTHOR: Shyu Kou-Gi (Reprint); Silver Marcy (Reprint); Magner Meredith (Reprint); Yancopoulos George D; Isner Jeffrey M (Reprint)
AUTHOR ADDRESS: St. Elizabeth's Med. Cent., Boston, MA, USA**USA
JOURNAL: Circulation 98 (17 SUPPL.): pI464 Oct. 27, 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998; 19981108
SPONSOR: The American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Angiopoietin-1 potentiates angiogenic response to vascular endothelial growth factor (VEGF) in hypercholesterolemic rabbit model with acute hindlimb ischemia
DESCRIPTORS:
MISCELLANEOUS TERMS: angiogenesis ;

6/3,K/33 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011801409 BIOSIS NO.: 199900061069
Gene therapy for myocardial angiogenesis: Initial clinical results with direct myocardial injection of phVEFG165 as sole therapy for myocardial ischemia
AUTHOR: Losordo Douglas W; Vale Peter R; Symes James F; Dunnington Cheryl H ; Esakof Darryl D; Maysky Michael; Ashare Alan B; Lathi Kishor; Isner Jeffrey M (Reprint)
AUTHOR ADDRESS: St. Elizabeth's Medical Center, 736 Cambridge St., Boston, MA 02135, USA**USA
JOURNAL: Circulation 98 (25): p2800-2804 Dec. 22-29, 1998 1998
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

Gene therapy for myocardial angiogenesis : Initial clinical results with direct myocardial injection of phVEFG165 as sole therapy for myocardial ischemia

...ABSTRACT: determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (VEGF) as sole therapy for patients with symptomatic myocardial ischemia . Methods and Results- VEGF gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who...

...these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding VEGF (phVEGF165) was injected directly into the ischemic myocardium via a mini left anterior thoracotomy. Injections caused no changes in heart rate (pre...

...the moment of injection. Serial ECGs showed no evidence of new myocardial infarction in any patient . Intraoperative blood loss was 0 to 50 cm3, and total chest tube drainage was 110...

...n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced ischemia was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients...

...5 patients. Conclusions- This initial experience with naked gene transfer as sole therapy for myocardial ischemia suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall...
...may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial ischemia.
DESCRIPTORS:
MISCELLANEOUS TERMS: myocardial angiogenesis

6/3,K/34 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011354195 BIOSIS NO.: 199800148442
Microvessel development following therapeutic angiogenesis with vascular endothelial growth factor (VEGF) in a rat model of hindlimb ischemia
AUTHOR: Takeshita S; Isshiki T; Miyazawa Y; Eto K; Ochiai M; Tanaka E; Mori H; Sato T
AUTHOR ADDRESS: Dep. Med., Teikyo Univ. Hosp., Tokyo, Japan**Japan
JOURNAL: Journal of the American College of Cardiology 31 (2 SUPPL. A): p 104A-105A Feb., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 47th Annual Scientific Session of the American College of Cardiology Atlanta, Georgia, USA March 29-April 1, 1998; 19980329
SPONSOR: The American College of Cardiology
ISSN: 0735-1097
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

Microvessel development following therapeutic angiogenesis with vascular endothelial growth factor (VEGF) in a rat model of hindlimb ischemia

DESCRIPTORS:
MISCELLANEOUS TERMS: angiogenesis ;

6/3,K/35 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010298759 BIOSIS NO.: 199698766592
VEGF expression in a mouse model of hind limb ischemia
AUTHOR: Couffinhal T; Silver M; Witzenbichler B; Sheriff D D; Isner J M
AUTHOR ADDRESS: St. Elizabeth's Med. Center, Tufts Univ. Sch. Med., Boston, MA 02135, USA**USA
JOURNAL: FASEB Journal 10 (3): pA578 1996 1996
CONFERENCE/MEETING: Experimental Biology 96, Part II Washington, D.C., USA April 14-17, 1996; 19960414
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

VEGF expression in a mouse model of hind limb ischemia
DESCRIPTORS:
MISCELLANEOUS TERMS: ANGIOGENESIS ;

6/3,K/36 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07529690 EMBASE No: 1999003076
Gene therapy for myocardial angiogenesis: Initial clinical results with direct myocardial injection of phVEGFinf 1inf 6$D5 as sole therapy for myocardial ischemia
Losordo D.W.; Vale P.R.; Symes J.F.; Dunnington C.H.; Esakof D.D.; Maysky M.; Ashare A.B.; Lathi K.; Isner J.M.
Dr. J.M. Isner, St. Elizabeth's Medical Center, 736 Cambridge St., Boston, MA 02135 United States
Circulation (CIRCULATION) (United States) 29 DEC 1998, 98/25 (2800-2804)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 19

Gene therapy for myocardial angiogenesis : Initial clinical results with direct myocardial injection of phVEGFinf 1inf 6$D5 as sole therapy...

...determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (VEGF) as sole therapy for patients with symptomatic myocardial ischemia . Methods and Results - VEGF gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who...

...these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding VEGF (phVEGFinf 1inf 6$D5) was injected directly into the ischemic myocardium via a mini left anterior thoracotomy. Injections caused no changes in heart rate (pre...

...the moment of injection. Serial ECGs showed no evidence of new

myocardial infarction in any patient . Intraoperative blood loss was 0 to 50 cmsup 3, and total chest tube drainage was...

...n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced ischemia was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients...

...5 patients. Conclusions - This initial experience with naked gene transfer as sole therapy for myocardial ischemia suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall...

...may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial ischemia.
MEDICAL DESCRIPTORS:
*heart muscle ischemia--surgery--su; *heart muscle ischemia--therapy--th; * angiogenesis

6/3,K/37 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07389720 EMBASE No: 1998301254
Expression of vascular endothelial growth factor (VEGF) and its receptors (Flt-1 and Flk-1) following permanent and transient occlusion of the middle cerebral artery in the rat
Lennmyr F.; Ata K.A.; Funa K.; Olsson Y.; Terent A.
Dr. F. Lennmyr, Department of Medicine, University Hospital, S-751 85 Uppsala Sweden
Journal of Neuropathology and Experimental Neurology (J. NEUROPATHOL. EXP. NEUROL.) (United States) 1998, 57/9 (874-882)
CODEN: JNENA ISSN: 0022-3069
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 55

Expression of vascular endothelial growth factor (VEGF) and its receptors (Flt-1 and Flk-1) following permanent and transient occlusion of the...

Vascular endothelial growth factor (VEGF) is a known endothelial mitogen and a potent enhancer of vascular permeability although its role in focal cerebral ischemia is still not completely understood. The present report describes the immunohistochemical distribution of VEGF and its 2 receptors, Flt-1 and Flk-1 at day 1 and 3 following permanent and transient middle cerebral artery occlusion (MCAO) in the rat . A bilateral increase in VEGF immunoreactivity, particularly in neurons and blood vessels, was seen in both the experimental designs by...

...side, where reaction was most prominent in the border zones of the infarcts. Immunoreaction to VEGF was more pronounced in cases of permanent MCAO than in transient MCAO. Flt-1 reaction...

...was present to some extent in endothelial cells. These findings indicate an early upregulation of VEGF and its receptors after permanent as well as transient focal cerebral ischemia in the rat.
MEDICAL DESCRIPTORS:
protein expression; drug receptor binding; immunohistochemistry; blood vessel permeability; immunoreactivity; glia cell; endothelium cell;

angiogenesis ; receptor upregulation; hypoxia; brain ischemia; nonhuman; rat; animal experiment; animal model; controlled study; article; priority ...

6/3,K/38 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07380372 EMBASE No: 1998285843
Increased vascular endothelial growth factor (VEGF) and transforming growth factorbeta (TGF(beta)) in experimental autoimmune uveoretinitis: Upregulation of VEGF without neovascularization
Vinores S.A.; Chan C.-C.; Vinores M.A.; Matteson D.M.; Chen Y.-S.; Klein D.A.; Shi A.; Ozaki H.; Campochiaro P.A.
S.A. Vinores, 825 Maumenee Building, Wilmer Ophthalmologic Institute, Johns Hopkins Univ. Sch. of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287-9289 United States
Journal of Neuroimmunology (J. NEUROIMMUNOL.) (Netherlands) 14 AUG 1998, 89/1-2 (43-50)
CODEN: JNRID ISSN: 0165-5728
PUBLISHER ITEM IDENTIFIER: S0165572898000757
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 59

Increased vascular endothelial growth factor (VEGF) and transforming growth factorbeta (TGF(beta)) in experimental autoimmune uveoretinitis: Upregulation of VEGF without neovascularization
...with S-antigen (S-Ag) to study the potential roles of vascular endothelial growth factor (VEGF) and the betainf 1 and betainf 2 isoforms of transforming growth factor (TGF(betainf 1) and TGF(betainf 2)) during the progression of the disease. VEGF has been implicated as an angiogenic factor in ischemic retinopathies; however, Lewis rats developing EAU have high levels of VEGF in the retina, but no neovascularization. In the present study, immunohistochemical staining for VEGF , TGF(betainf 1) and TGF(betainf 2) was performed on the retinas of Lewis rats developing EAU or with oxygen-induced ischemic retinopathy. In rats immunized with S-antigen, a marked upregulation of VEGF was immunohistochemically visualized from the inner nuclear layer to the inner limiting membrane prior to blood-retinal barrier (BRB) failure and lymphocytic infiltration. VEGF is normally induced by hypoxia and its induction leads to neovascularization. Coincident with the increase in VEGF , there was increased immunoreactivity for TGF(betainf 1) and TGF(betainf 2) within the same layers of the retina. In contrast, rats with ischemic retinopathy and retinal neovascularization showed only a modest increase in VEGF immunoreactivity, which is largely confined to retinal ganglion cells and inner retinal vessels, and little...

...abrupt onset as it does in rats and may involve neovascularization, a comparable upregulation of VEGF in the inner retina to that seen in rats developing EAU occurs with no increase...

...inhibit endothelial cell proliferation, it is likely that an increase in TGF(beta) may prevent VEGF from exerting its endothelial growth activity in the rat EAU model, but VEGF may be operative in inducing BRB failure. These data suggest that there is a complex...
MEDICAL DESCRIPTORS:
retinitis--etiology--et; uveitis--etiology--et; autoimmune disease --etiology--et; angiogenesis ; blood vessel permeability; retina blood

vessel; retina neovascularization; immunohistochemistry; nonhuman; female; rat; animal model; controlled...

6/3,K/39 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07148840 EMBASE No: 1998027211
Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization
Amano S.; Rohan R.; Kuroki M.; Tolentino M.; Adamis A.P.
A.P. Adamis, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114 United States
Investigative Ophthalmology and Visual Science (INVEST. OPHTHALMOL. VIS. SCI.) (United States) 1998, 39/1 (18-22)
CODEN: IOVSD ISSN: 0146-0404
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 28

PURPOSE. Vascular endothelial growth factor (VEGF) is required for vascular development and for ischemia -related tumor, iris, and retinal neovascularization. The role of VEGF in inflammatory corneal neovascularization is unknown and was investigated in these studies. METHODS. A rat model was used in which removal of the corneal and limbal epithelium resulted in circumferential neovascularization. Corneal VEGF mRNA levels were quantified with ribonuclease protection assays, and VEGF protein was studied in situ using immunohistochemical analysis. Controlled-release pellets containing anti- VEGF antibodies were implanted into the corneal stroma and were used to determine the requirement for VEGF in corneal neovascularization. RESULTS. VEGF mRNA and protein were induced to high levels after corneal injury and were temporally and spatially correlated with inflammation and neovascularization. VEGF immunoreactivity was localized primarily to the inflammatory cells invading the wounded cornea. The specific inhibition of VEGF bioactivity with neutralizing antibodies potently suppressed corneal neovascularization. CONCLUSIONS. These data are the first to demonstrate that VEGF may be required for inflammatory neovascularization of the rat cornea and to identify VEGF as a functional endogenous corneal angiogenic factor.
MEDICAL DESCRIPTORS:
wound healing; cornea epithelium; angiogenesis ; pathogenesis; nonhuman; rat; animal model; animal tissue; article; priority journal

6/3,K/40 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

07055146 EMBASE No: 1997336990
Intracerebral tumor-associated hemorrhage caused by overexpression of the vascular endothelial growth factor isoforms VEGFinf 1inf 2inf 1 and VEGFinf 1inf 6$D5 but not VEGFinf 1inf 8inf 9
Cheng S.-Y.; Nagane M.; Huang H.-J.S.; Cavenee W.K.
W.K. Cavenee, Ludwig Institute for Cancer Research, San Diego Branch, University of California, 9500 Gilman Drive, San Diego, CA 92093-0660 United States
Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1997, 94/22 (12081-12087)

CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

The vascular endothelial growth factor (VEGF) has been shown to be a significant mediator of angiogenesis during a variety of normal and pathological processes, including tumor development. Human US7MG glioblastoma cells express the three VEGF isoforms: VEGFinf 1inf 2inf 1, VEGFinf 1inf 6$D5, and VEGFinf 1inf 8inf 9. Here, we have investigated whether these three isoforms have distinct roles in glioblastoma angiogenesis . Clones that overexpressed each isoform were derived and inoculated into mouse brains. Mice that received VEGFinf 1inf 2inf 1- and VEGFinf 1inf 6$D5-overexpressing cells...

...none on the border of the tumors caused by the parental cells. Thus, by introducing VEGF -overexpressing glioblastoma cells into the brain, we have established a reproducible and predictable in vivo...

...of single molecular species. Such a model should be useful for uncovering the role of VEGF isoforms in the mechanisms of angiogenesis and for investigating intracerebral hemorrhage due to ischemic stroke or congenital malformations.
MEDICAL DESCRIPTORS:
angiogenesis ; animal cell; article; controlled study; glioblastoma --etiology--et; growth regulation; human; human cell; molecular cloning...

6/3,K/41 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06315608 EMBASE No: 1995353353
VEGFinf 1inf 6$D5 expressed by a replication-deficient recombinant adenovirus vector induces angiogenesis in vivo
Muhlhauser J.; Merrill M.J.; Pili R.; Maeda H.; Bacic M.; Bewig B.; Passaniti A.; Edwards N.A.; Crystal R.G.; Capogrossi M.C.
Gerontology Research Center, National Institute on Aging, National Institutes of Health, 4940 Eastern Ave.,Baltimore, MD 21224 United States
Circulation Research (CIRC. RES.) (United States) 1995, 77/6 (1077-1086)
CODEN: CIRUA ISSN: 0009-7330
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

VEGFinf 1inf 6$D5 expressed by a replication-deficient recombinant adenovirus vector induces angiogenesis in vivo

...of angiogenic factors via virus-mediated gene transfer may be useful in the treatment of ischemic disorders, the replication deficient adenovirus (Ad) vector AdCMV.VEGFinf 1inf 6$D5 (where CMV is cytomegalovirus and VEGF is vascular endothelial growth factor) containing the cDNA for human VEGFinf 1inf 6$D5, a...

...endothelial cell- specific angiogenic growth factor, was constructed. Human umbilical vein endothelial cells (HUVECs) and rat aorta smooth muscle cells (RASMCs) infected with AdCMV.VEGFinf 1inf 6$D5 (5 and 20 plaque-forming units (pfu) per cell) demonstrated VEGF mRNA expression and protein secretion into the supernatant. Furthermore, the conditioned

medium from these cells enhanced vascular permeability in vivo. In contrast, neither VEGF mRNA nor secreted protein was found in uninfected HUVECs or RASMCs or in cells infected...

...was resuspended in 0.5 mL Matrigel and injected subcutaneously into mice. Immunohistochemical staining demonstrated VEGF in the tissues surrounding the Matrigel plugs containing AdCMV.VEGFinf 1inf 6$D5 up to 3 weeks after injection, whereas no VEGF was found in the control plugs with AdCMV.betagal. Two weeks after injection, there was...

...in the tissues surrounding the Matrigel containing AdCMV.VEGFinf 1inf 6$D5, whereas no significant angiogenesis was observed in response to AdCMV.betagal. Furthermore, the Matrigel plugs with AdCMV.VEGFinf 1inf...

...useful strategy for efficient local delivery of VEGFinf 1inf 6$D5 in the treatment of ischemic diseases.
MEDICAL DESCRIPTORS:
* angiogenesis ; *neovascularization (pathology)

6/3,K/42 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06019986 EMBASE No: 1995050117
Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal neovascularization
Pierce E.A.; Avery R.L.; Foley E.D.; Aiello L.P.; Smith L.E.H.
Department of Ophthalmology, Children's Hospital, 300 Longwood Avenue,Boston, MA 02115 United States
Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1995, 92/3 (905-909)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...been fully identified. To investigate the role of vascular endothelial growth factor/vascular permeability factor (VEGF /VPF) in retinal neovascularization, the expression of VEGF /VPF mRNA and protein were studied in a mouse model of proliferative retinopathy. RNA (Northern) blot analysis revealed that retinal VEGF /VPF mRNA expression increased 3-fold between 6 and 12 hr of relative retinal hypoxia and remained elevated during the development of neovascularization. In situ hybridization localized VEGF /VPF mRNA to cells bodies in the inner nuclear layer of the retina. Immunohistochemical confocal microscopy demonstrated that VEGF /VPF protein levels increase with a time course similar to that of the mRNA. The cells in the inner nuclear layer of the retina that produce VEGF /VPF were identified morphologically as Muller cells. These data suggest that VEGF /VPF expression in the retina plays a central role in the development of retinal ischemia - induced ocular neovascularization.
MEDICAL DESCRIPTORS:
angiogenesis ; animal experiment; animal model; animal tissue; article; gene expression; hypoxia; immunohistochemistry; in situ hybridization; mouse...
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Set Items Description

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S1      105658   (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR
              MOUSE OR RAT OR RABBIT OR PATIENT)
S2        1556   S1 AND (ANGIOGENESIS)
S3         293   S2 NOT PY>1999
S4         125   S3 AND (GM-CSF OR G-CSF OR M-CSF OR VEGF)
S5          57   RD  (unique items)
S6          42   S5 NOT PY>1998
S7           0   S3 AND (SCF OR SDF-1)
S8           1   S3 AND (ANGIOPOIETIN-1 OR ANGIOPOIETIN-2 OR (FLT-3 (W) LIG-
               AND))
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